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REVIEW

Pulse oximetry: Understanding its basic principles facilitates appreciation of its limitations

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Summary
Pulse oximetry has revolutionized the ability to monitor oxygenation in a continuous, accurate, and non-invasive fashion. Despite its ubiquitous use, it is our impression and supported by studies that many providers do not know the basic principles behind its mechanism of function. This knowledge is important because it provides the conceptual basis of appreciating its limitations and recognizing when pulse oximeter readings may be erroneous. In this review, we discuss how pulse oximeters are able to distinguish oxygenated hemoglobin from deoxygenated hemoglobin and how they are able to recognize oxygen saturation only from the arterial compartment of blood. Based on these principles, we discuss the various conditions that can cause spurious readings and the mechanisms underlying them.
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Basic principles of function

The pulse oximeter has revolutionized modern medicine with its ability to continuously and transcutaneously monitor the functional oxygen saturation of hemoglobin in arterial blood (SaO_2). Pulse oximetry is so widely prevalent in medical care that it is often regarded as a fifth vital sign.[1] It is important to understand how the technology functions as well as its limitations because erroneous readings can lead to unnecessary testing.[2] Frequent false alarms in the intensive care unit can also undermine patient safety by distracting caregivers. To recognize the settings in which pulse oximeter readings of oxygen saturation (SpO_2) may result in false estimates of the true SaO_2, an understanding of two basic principles of pulse oximetry is required: (i) how oxyhemoglobin (O_2Hb) is distinguished from deoxyhemoglobin (HHb) and (ii) how the SpO_2 is calculated only from the arterial compartment of blood.

Pulse oximetry is based on the principle that O_2Hb and HHb differentially absorb red and near-infrared (IR) light. It is fortuitous that O_2Hb and HHb have significant differences in absorption at red and near-IR light because these two wavelengths penetrate tissues well whereas blue, green, yellow, and far-IR light are significantly absorbed by non-vascular tissues and water.[3] O_2Hb absorbs greater amounts of IR light and lower amounts of red light than does HHb; this is consistent with experience — well-oxygenated blood with its higher concentrations of O_2Hb appears bright red to the eye because it scatters more red light than does HHb. On the other hand, HHb absorb more red light and appears less red. Exploiting this difference in light absorption properties between O_2Hb and HHb, pulse oximeters emit two wavelengths of light, red at 660 nm and near-IR at 940 nm from a pair of small light-emitting diodes located in one arm of the finger probe. The light that is transmitted through the finger is then detected by a photodiode on the opposite arm of the probe; *i.e.*, the relative amount of red and IR light absorbed are used by the pulse oximeter to ultimately determine the proportion of Hb bound to oxygen.

The ability of pulse oximetry to detect SpO_2 of only arterial blood is based on the principle that the amount of red and IR light absorbed fluctuates with the cardiac cycle, as the arterial blood volume increases during systole and decreases during diastole; in contrast, the blood volume in the veins and capillaries as well as the volumes of skin, fat, bone, etc, remain relatively constant. A portion of the light that passes through tissues without being absorbed strikes the probe's photodetector and, accordingly, creates signals with a relatively stable and non-pulsatile "direct current" (DC) component and a pulsatile "alternating current" (AC) component (Fig. 1A). A cross-sectional diagram of an artery and a vein during systole and diastole illustrates the non-pulsatile (DC) and pulsatile (AC) compartments of arteries and the relative absence of volume change in veins and capillaries (Fig. 1B). Pulse oximeters use amplitude of the absorbances to calculate the Red:IR Modulation Ratio

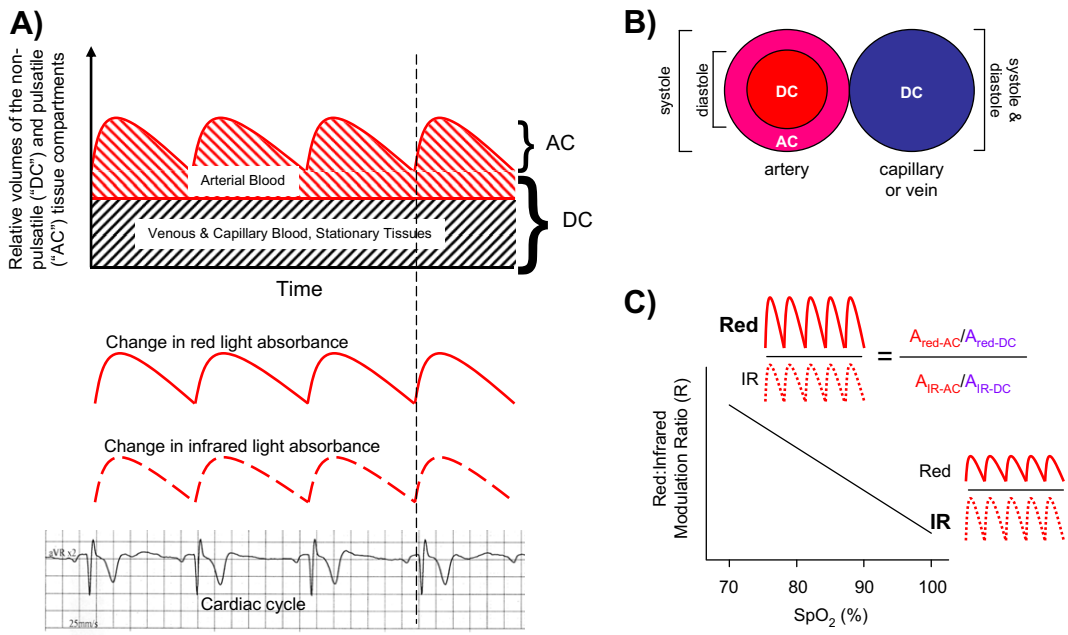

Figure 1 Schematic diagram of light absorbance by a pulse oximeter. (A) In a person with good cardiac function, the onset of the cardiac systole, as denoted by the onset of the QRS complex coincides with the onset in the increase of the arterial blood volume. The amount of red and IR light absorbed in the arterial compartment also rises and fall with systole and diastole, respectively, due to the increase and decrease in blood volume. The volume that increases with systole is also known as the pulsatile or "alternating current" (AC) compartment and the compartment in which the blood volume does not change with the cardiac cycle is known as the non-pulsatile or "direct current" (DC) compartment. (B) A cross-sectional diagram of an artery and a vein displaying the pulsatile (AC) and non-pulsatile (DC) compartments of the blood vessels. Note that only the artery has a pulsatile (AC) component. (C) A diagram of a calibration (standard) curve of the Red:IR Modulation Ratio in relation to the SpO_2. Increased red light absorbance (increased R) is associated with increased deoxyhemoglobin, *i.e.*, lower SpO_2. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(R)[4]; *i.e.*, $R = (A_{red,AC}/A_{red,DC})/(A_{IR,AC}/A_{IR,DC})$ where A = absorbance; in other words, R is a double-ratio of the pulsatile and non-pulsatile components of red light absorption to IR light absorption. At low arterial oxygen saturations, where there is increased HHb, the relative change in amplitude of the red light absorbance due to the pulse is greater than the IR absorbance, *i.e.*, $A_{red,AC} > A_{IR,AC}$ resulting in a higher R value; conversely, at higher oxygen saturations, $A_{IR,AC} > A_{red,AC}$ and the R value is lower (Fig. 1C). A microprocessor in pulse oximeters uses this ratio (calculated over a series of pulses) to determine the SpO_2 based on a calibration curve that was generated empirically by measuring R in healthy volunteers whose saturations were altered from 100% to approximately 70%[5] (Fig. 1C). Thus, SpO_2 readings below 70% should not be considered quantitatively reliable although it is unlikely any clinical decisions would be altered based on any differences in SpO_2 measured below 70%.[3,6]

How pulse oximeters exclude the influence of venous and capillary blood and other stationary tissues from the calculation of SpO_2 can be conceptually understood by examining the Beer–Lambert Law of absorbance. According to the Beer–Lambert Law as applied to a modeled blood vessel, $A = \varepsilon bc$ where A = absorbance, ε = absorption (or extinction) coefficient of hemoglobin at a specified wavelength (a combination of the O_2Hb and HHb coefficients), b = pathlength traveled by the emitted light through the blood vessel, and c = concentration of Hb. Simply measuring absolute absorbance would be an inaccurate estimate of arterial SpO_2 since elevated levels of HHb in the venous blood would also contribute to the measured value. However, a pulse oximeter is able to determine only arterial SpO_2 by measuring *changes* in absorbance over time. To illustrate this concept mathematically, the total absorbance (A_t) can be thought of as a linear combination of venous (A_v) and arterial (A_a) absorbances ($A_t = A_v + A_a = \varepsilon_v b_v c_v + \varepsilon_a b_a c_a$). Since pulse oximeters measure absorbance with respect to time, the derivative of the previous equation becomes $dA_t/dt = d(\varepsilon_v b_v c_v)/dt + d(\varepsilon_a b_a c_a)/dt$. Since ε and c are constants (note that ε can vary depending on the wavelength of light, but is a constant for any particular wavelength and Hb species), the previous equation simplifies to $dA_t/dt = (db_v/dt)(\varepsilon_v c_v) + (db_a/dt)(\varepsilon_a c_a)$. Since arteries dilate and constrict much more than veins, *i.e.*, the change in $b_a \gg$ the change in b_v ($db_a/dt \gg db_v/dt$), we can assume b_v as a constant and $db_v/dt = 0$; hence, the previous equation simplifies to $dA_t/dt = (db_a/dt)(\varepsilon_a c_a)$, or equivalently $\Delta A_t = \Delta A_a$; in other words, the change in A_t measured = change in absorbance due to the arterial blood content with little or no contribution by the venous blood. Therefore, an adequate pulse is necessary for pulse oximeters to work and is the basis for the well-known fact that attempting to measure SpO_2 in regions with little or no blood perfusion will result in absent or inaccurate readings.[4] These principles can be used to help explain certain behaviors of pulse oximetry, as will be discussed further below.

Pros and cons of different types of pulse oximeter probes

The reason pulse oximeter probes interrogate the finger, nose, ear lobe, and forehead is that the skin in these areas have a much higher vascular density than, for example, the skin of the chest wall.[4] Reusable clip probes (finger, nasal, ear) and single-patient adhesive probes (finger, forehead) are the two main types of pulse oximeter probes. Advantages of the reusable clip probes are the rapidity in which they can be employed, the ease in which different body sites can sampled in the event of low amplitude waves, and cost-effectiveness in outpatient settings where multiple patients can be measured sequentially with one probe because only a single reading of SpO_2 is required. Advantages of the single-patient adhesive probes are potentially less transmission of nosocomial infections, more secure placement when there is excessive patient movement, and ability to monitor sites other than the acral regions since the latter areas are more vulnerable to vasoconstriction. Thus, for continuous monitoring of SpO_2, one particular type of probe may be more appropriate than others depending on the clinical circumstance; *i.e.*, some "trial-and-error" may be necessary to find the optimal probe. For example, in hypotensive, vasoconstricted patients, ear and forehead probes may be more reliable as these areas are less likely to vasoconstrict than the fingers in response to endogenous and exogenous catecholamines.[3,7] In hypothermia, where there is secondary vasoconstriction, the forehead probe has been shown to be more reliable than the finger probe.[8,9]

Even after optimizing the type of probe, false readings of SpO_2 may occur in various settings and medical conditions. In the following sections, we discuss the causes and mechanisms of unreliable SpO_2 readings, summarized in Table 1. We close with a discussion on rarer instances in which the SpO_2 may actually be more reliable than SaO_2 readings in measuring arterial oxygen saturation.

Causes of intermittent drop-outs or inability to read SpO_2

It is common knowledge that an attenuated and/or inconsistent wave tracing generated by pulse oximeters displayed on intensive care unit monitors is an indication that the SpO_2 reading is unreliable or may become so, *i.e.*, increased drop outs or false transient SpO_2 changes. The amplitude of such a pulse oximeter waveform reflects the amount of cardiac-induced light modulation, as noted by the near simultaneous onset of the QRS complex on the electrocardiogram with the onset of the positive deflection of the pulse oximetry wave tracing (Fig. 1A). Although portable pulse oximeters do not typically have such wave tracings, they often have a pulse signal bar that shows the level of change in light absorbance (and thus strength of the pulse) to indicate the possibility of a suboptimal reading.

Low-amplitude pulse oximetry wave tracings may be due to poor finger perfusion resulting from vasoconstriction and/or hypotension from a number of causes including distributive or hypovolemic shock, hypothermia, use of vasoconstrictor agents, and poor cardiac output due to pump failure or dysrhythmia. Arterial compression (*e.g.*, pumped-up sphygmomanometer) or arterial blockage proximal to probe placement (*e.g.*, peripheral vascular disease) can also result in poor pulse oximetry wave tracings. Decreased pulse amplitude in the arterial blood signal additionally decreases the pulse oximeter's signal to noise ratio and potentially result in the inability to post values, intermittent drop-outs and alarms, and unstable SpO_2 readings. Knowing that the aforementioned conditions can result in false SpO_2 readings is the single best deterrent to accepting falsely low SpO_2 readings. While clinical assessment can help differentiate spurious from true SpO_2 readings, uncertain cases should be corroborated by arterial blood gas analysis.

Table 1 Causes and mechanisms of unreliable SpO_2 readings.

1. Causes of intermittent drop-outs or inability to read SpO_2
   - Poor perfusion due to a number of causes, *e.g.*, hypovolemia, vasoconstriction, etc
2. Causes of falsely normal or elevated SpO_2
   - Carbon monoxide poisoning
   - Sickle cell anemia vasoocclusive crises (overestimation of FO_2Hb and underestimation of SaO_2)
3. Causes of falsely low SpO_2
   - Venous pulsations
   - Excessive movement
   - Intravenous pigmented dyes
   - Inherited forms of abnormal hemoglobin
   - Fingernail polish
   - Severe anemia (with concomitant hypoxemia)
4. Causes of falsely low or high SpO_2
   - Methemoglobinemia
   - Sulfhemoglobinemia
   - Poor probe positioning
   - Sepsis and septic shock
5. Causes of falsely low FO_2Hb as measured by a co-oximeter
   - Severe hyperbilirubinemia
   - Fetal Hb (HbF)

Causes of falsely normal or elevated SpO_2

Carbon monoxide poisoning

Carbon monoxide (CO) is an odorless, colorless, tasteless, and non-irritating gas. Since patients with CO poisoning may present with signs and symptoms that are non-specific (*e.g.*, headaches), mimics of other disorders (*e.g.*, food poisoning, alcohol intoxication, acute psychiatric decompensation, or "flu-like symptoms"), or with genuine disorders that are precipitated by CO toxicity (*e.g.*, angina, syncope), the diagnosis is often missed with occult exposure. CO toxicity may be due to exposure from a variety of sources including propane-powered engine, natural gas, automobile exhaust, portable generators, gas log fireplaces, kerosene heaters, fire smoke, and paint strippers and spray paints as dichloromethane in these products gets metabolized to CO. The principal pathogenic mechanism of CO poisoning is the strong avidity of CO for Hb (240× greater than O_2), forming carboxyHb (COHb), reducing the O_2 carrying capacity of Hb and precipitating tissue hypoxemia. CO can also impair myoglobin and mitochondrial function; increase guanylate cyclase activation which can lead to vasodilation and hypotension; and augment lipid peroxidation causing microvascular impairment and reperfusion injury.

While *considering* the possibility of CO poisoning in the differential diagnosis is a linchpin in recognizing its presence in an ill patient, the diagnosis must be made objectively. Because O_2Hb and COHb absorb red light (660 nm) similarly and COHb absorbs very little near-IR light (940 nm) (Fig. 2), the photodiode of standard pulse oximeters — that only emit red and near-IR light — cannot differentiate between O_2Hb and COHb. The similar absorptive property of O_2Hb and COHb for red light is consistent with the clinical observation that patients with carboxyhemoglobinemia can appear bright red and not cyanotic.[10] In the context of *R*, because COHb will decrease both HHb and O_2Hb concentrations, the normally greater red light absorption by HHb will be decreased but the red light absorption of the *combined* O_2Hb and COHb species will be maintained or slightly increased. However, because HHb still absorbs red light better than either COHb or O_2Hb, the reduction in HHb in the presence of carboxyhemoglobinemia results in a net effect of decreased red light absorption and *R* that is reduced more than predicted (see Fig. 1C), resulting in SpO_2 that overestimates the *fractional* O_2Hb content (FO_2Hb), which is also measured by co-oximeters but in contrast to SaO_2, takes into account COHb concentrations. Thus, in significant carboxyhemoglobinemia, standard pulse oximeters can give a false normal (or elevated) SpO_2 when in fact the FO_2Hb is low. Semantically, it is important to emphasize that it is the FO_2Hb content and not the SaO_2 that is decreased by COHb (see Box 1). For pulse oximeters to be able to detect COHb as well as O_2Hb and HHb, an instrument with at least three light beams of different wavelengths would have to be employed[10]; while they exist, they are not widely available.

Sickle cell anemia vasoocclusive crises

Complications of sickle cell disease, such as vasoocclusive crisis and acute chest syndrome, are often precipitated or exacerbated by hypoxemia, and can result in a vicious cycle of additional sickling and vasoocclusive crises.[11] Thus, accurate detection of hypoxemia in these patients plays an important role in mitigating further red blood cell sickling. The accuracy of pulse oximetry in monitoring oxygenation in sickle cell disease has been debated. In a study of 17 patients with sickle cell disease, SpO_2 was found to overestimate FO_2Hb content by an average of 3.4% and to underestimate SaO_2 by an average of 1.1%.[12] However, these minor biases in pulse oximeter readings did not lead to a misdiagnosis of either normoxemia or hypoxemia. Similarly, a study of 24 patients with sickle cell disease determined that SpO_2 underestimated SaO_2 readings by 1.6%; this difference was clinically insignificant.[13] However, the authors note that while SpO_2 may be used as an accurate representation of SaO_2 in sickle cell disease, the FO_2Hb may be a more useful measurement, as some individuals with sickle cell disease may have elevated COHb (due to the metabolism of heme to bilirubin and CO, as discussed below); in these instances, SpO_2 overestimates the FO_2Hb, as discussed in Box 1. Other studies additionally suggest that SpO_2 overestimation of FO_2Hb and underestimation of SaO_2 become more significant during vasoocclusive crises.[14,15]

Box 1. Difference between fractional O_2Hb content and SaO_2.

In blood gas analysis, the SaO_2, often denoted in the literature as *functional* SaO_2, is defined as $[O_2Hb]/([O_2Hb] + [HHb])$. Based on this equation, the presence of a dyshemoglobin such as COHb should not affect the SaO_2. Accordingly, it is not correct to state that the functional SaO_2 is lowered by COHb. Rather, it is the *fractional* O_2Hb content (often abbreviated FO_2Hb), also known as *fractional* SaO_2, that is lowered by COHb since $FO_2Hb = [O_2Hb]/([O_2Hb] + [HHb] + [COHb] + [MetHb])$ where [MetHb] = methemoglobin concentration in blood. Co-oximeter reports typically contain both "SaO_2" (meaning functional SaO_2) as well as FO_2Hb (meaning fractional SaO_2 although the term fractional O_2Hb *content* is used to avoid confusion). Thus, both functional SaO_2 and SpO_2 are minimally affected by COHb, even up to 40% COHb.[54] In a study of CO exposure in experimental animals, a SpO_2 level of 90% was recorded when a simultaneous COHb level was 70% and a FO_2Hb saturation was 30%.[55] Thus, even in significant CO poisoning, both functional SaO_2 and SpO_2 will give a "false normal" indication of oxygenation whereas the O_2 carrying capacity of Hb, as indicated by FO_2Hb, is alarmingly reduced. This distinction between SaO_2 and FO_2Hb is illustrated schematically in Fig. 3 and is analogous to erroneously concluding that because a severely anemic patient has a normal SaO_2, it indicates that the O_2 carrying capacity in the blood is adequate.

Another important caveat with oxygen saturation determination in sickle cell patients is that under normoxic conditions, where there is little HbS polymerization, HbS affinity for oxygen is similar to the normal HbA. However, in the presence of conditions that precipitates sickling, including hypoxemia, HbS has less affinity for oxygen and the oxygen-Hb dissociation curve is shifted to the right, *i.e.*, for any given PaO_2, the SaO_2 is lower.[16,17] Teleologically, this shift is advantageous to increase oxygen unloading to tissues.

Causes of falsely low SpO_2

Venous pulsations

Venous pulsations, causing a significant change in venous volume with each cardiac cycle, can contribute to a falsely low SpO_2 reading because venous O_2Hb saturation (SvO_2) is now also measured by the pulse oximeter, artificially lowering the arterial saturation. Venous pulsations can occur when adhesive fingerprobes are placed too tightly around the finger, in severe tricuspid regurgitation, when the location of the probes are in dependent positions (*e.g.*, probe on the forehead with the patient in a Trendelenburg position), and possibly in distributive shock where widespread vasodilation results in physiologic arteriovenous shunting.[18,19] When venous pulsations is considered to be occurring with a forehead sensor in a patient requiring the supine or Trendelenburg position, an elastic-tensioned headband applied to the forehead sensor can significantly reduce the occurrence of falsely low SpO_2 readings.[20]

Excessive movement

Excessive movement such as tremor or convulsions has been documented to cause spuriously low SpO_2, with desaturations below 50% sometimes observed,[21,22] though less commonly SpO_2 overestimations can also occur. In theory, motion can cause the normally static tissues in relation to the sensor position to change over the time frame of the arterial pulses. At times, this motion can augment or mimic the cardiac-induced signals as the blood in the veins (and other previously stationary tissues) are now moving, further modulating the red and IR light attenuation in the probed tissue (see Box 2). However, many newer generation pulse oximeters have improved processing algorithms that reduce the occurrence of false SpO_2 readings due to excessive patient movements.[21,22]

Intravenous pigmented dyes

Pigmented dyes are used medically or as agents in various medical diagnostic tests; *e.g.*, the principal medicinal use of methylene blue is in methemoglobinemia where it serves as a reducing agent. Methylene blue has also been used as a dye in endoscopic polypectomy where it is injected into the submucosa around the polyp to be removed, marking the site in the event additional tissues need to be excised. Indigo carmine (FD&C Blue#2)-based dye is infrequently used to detect amniotic fluid leaks as well as to detect leaks in the urinary system during surgery since intravenous indigo carmine is cleared rapidly by the kidneys. Iodocyanine green is used for various medical diagnostic tests such as

Box 2. Extremely low SpO_2 with no dyspnea.

A 93 year-old man was hospitalized for a non-ST elevation myocardial infarction after an episode of gastroenteritis. He lived independently, shopping for himself and driving his car without incident. He was a lifetime non-smoker and drank one beer per week. His past medical history was notable for essential tremor, hypothyroidism, benign prostatic hypertrophy, stage 4 chronic renal disease but not on dialysis, glaucoma, and venous thromboembolism three years ago. On examination, he was in no acute distress and looked much younger than stated age. His temperature was 97.1 °F, pulse 80 beats per minute, blood pressure 125/60 mmHg, respiratory rate 16 per minute, and a SpO_2 of 93% on baseline supplemental oxygen of 2 L/min. Exam only notable for a mild resting hand tremor.

He underwent a dipyridamole-^{99m}Tc-sestamibi nuclear perfusion study. Upon returning from the stress test to his room, vital signs taken by a nursing student using a wall-mounted pulse oximeter revealed a pulse rate of 228 beats per minute and SpO_2 reading of 73%. He was placed on high flow oxygen by face mask and a Rapid-Response Medical Team was called. Due to the persistently low SpO_2, he was placed on 100% oxygen using a non-rebreather mask but the SpO_2 remained between 40 and 70% and the heart rate on the monitor remained above 200 beats per minute. His measured blood pressure was 135/80 mmHg. He denied any chest pains or any change in his breathing. He appeared nervous but was not cyanotic. His lungs were clear to auscultation. An EKG rhythm strip was obtained and shows a baseline heart rate of 60 beats per minute with smaller spikes between the QRS complexes, best seen in lead II (Fig. 4). These low voltage spikes are due to his hand tremor and the measured SpO_2 with the finger probe was considered to be spuriously low due to the hand tremor. This assumption was consistent with the observation that the pulse reading of $\geq$200 beats per minute by the oximeter was similar to the tremor rate on the EKG. Using a different pulse oximeter in which the probe was placed on his forehead, the pulse rate was 65 beats per minute and the simultaneous SpO_2 was 100% while breathing high flow oxygen through a non-rebreather mask. For confirmation, an arterial blood gas obtained on 100% non-rebreather mask revealed a pH of 7.36, $PaCO_2$ of 41 mmHg, PaO_2 of 302 mmHg, and a SaO_2 of 100%. At the time that the arterial blood gas was obtained, the simultaneous SpO_2 reading using the finger probe was 48%. In retrospect, auscultation of the heart beat and/or palpation of a radial pulse revealing that the heart rate was not $>$200 beats per minute would have quickly indicated that the pulse oximetry reading of the SpO_2 was inaccurate.

determination of hepatic function and liver blood flow, and for ophthalmic angiography.

Peak light absorption of methylene blue is 668 nm (Fig. 5), very close to the strong red light absorption by HHb, resulting in a higher *R* value and mimicking HHb.[23] Hence, administration of methylene blue into the blood stream can falsely reduce SpO_2 readings. In human volunteers with normal baseline SpO_2 ($\geq$97%), a profound drop in SpO_2 occurred following intravenous administration of 5 mL of 1% methylene blue with a median nadir SpO_2 of 65% although there was a wide range in SpO_2 reduction among the subjects.[23] Indocyanine green and indigo carmine do not have as great absorption for red light (Fig. 5). This is consistent with the finding that intravenous injection of indocyanine green had only a minor decrease of ~3–4% in SpO_2 using a finger probe and intravenous injection of indigo carmine resulted in little or no change in SpO_2.[23]

Inherited forms of abnormal hemoglobin

Uncommon Hb variants have been reported to cause spuriously decreased SpO_2 readings, including Hb Lansing,[24] Hb Bonn,[25] Hb Koln,[26,27] Hb Hammersmith,[28] and Hb Cheverly.[29] Sarikonda et al.[24] reported a father and daughter with SpO_2 readings that were more than 10% lower than SaO_2 measurements due to an abnormal Hb variant (Hb Lansing) which accounted for ~11% of their total Hb. Assessment of oxygen affinity was normal, suggesting that interference of absorbance of red and/or near-IR light by the abnormal Hb accounted for the spurious reduction in SpO_2.[24] A father and son were reported to have falsely low SpO_2 due to mutation of the *ALPHA-Hb* gene in which resulted in a histidine-to-aspartatic acid substitution (Hb Bonn).[25] Hb Bonn was found to have a peak absorption at 668 nm (same as methylene blue), very close to the red light wavelength of 660 nm.[25] Hence, in the context of *R*, Hb Bonn causes an enhanced red light absorption, resulting in an elevated *R* value and lower SpO_2 measurement; in other words, Hb Bonn behaves like HHb and methylene blue. Similarly, Hb Cheverly spectra showed that the red light absorbance for this abnormal Hb was greater than for HbA.[29] Absorption spectra for both O_2Hb and HHb for a patient with 5.4% Hb Koln found red light absorbance was greater for Hb Koln than for HbA, indicating that *R* would be biased positively, falsely lowering SpO_2.[27]

Fingernail polish

Earlier reports of pulse oximeters noted that fingernail polish, particularly black, blue, and green color, can lower SpO_2 by up to 10%.[30,31] More recent studies with newer models of pulse oximeters found that fingernail polish has only a minor effect on SpO_2 readings; *i.e.*, black and brown fingernail polish displayed the greatest reduction in the SpO_2 reading but by an average decrease of $\leq$2%.[32,33]

Severe anemia (with concomitant hypoxemia)

Theoretically, anemia should not have much effect on SpO_2 readings since both O_2Hb and HHb would be proportionately affected. However, it has been observed that severe anemia can spuriously affect SpO_2.[34,35] Mechanistically, this is because scatter of visible and near-IR light by human tissues is not accounted for by the simplified Beer–Lambert equation, which assumes a single, well-defined light path.[4,36] This light scatter would be affected by the number of red blood cells; *i.e.*, in anemia, there would be less light scatter whereas calibration curves are derived from healthy individuals without anemia. Thus, with change in Hb content, the pathlength for the transmitted red and near-IR light would be altered, creating a bias in *R* and SpO_2 readings.

In an experimental study of dogs, SpO_2 was found to be an accurate representation of SaO_2 readings down to a hematocrit range of 10–14%. When the hematocrit dropped below 10%, the accuracy of the pulse oximeter deteriorated, underestimating co-oximeter readings by an average of 5.4%.[37] These findings were corroborated in a human study where in hypoxemic patients, the presence of anemia caused the SpO_2 to further underestimate the SaO_2.[38] In contrast, for normoxic individuals, severe anemia had minimal impact on SpO_2 values.[38–40] While the mechanistic explanation for this phenomenon is complicated and beyond the scope of this review, it is important to emphasize that *anemia per se does not cause a spuriously low SpO_2 but rather causes the SpO_2 to underestimate the SaO_2 in patients with true hypoxemia, but has little impact on SpO_2 measurements in normoxic individuals*. Since SpO_2 is underestimated in those with bona fide hypoxemia in the presence of severe anemia, this direction of error is fortuitous since earlier warning of hypoxemia by SpO_2 measurements will result in more timely administration of supplemental oxygen.

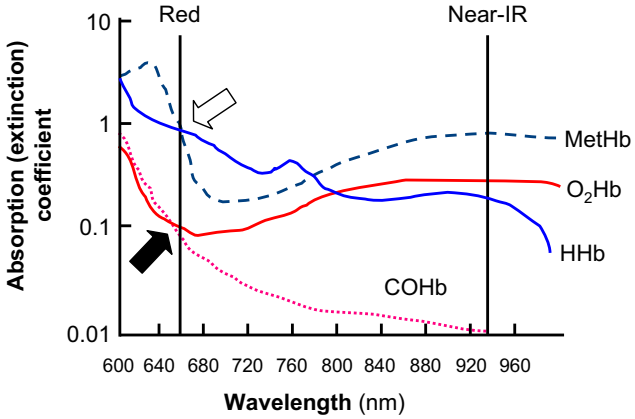

Figure 2 Absorption spectra for O_2Hb, HHb, COHb, and MetHb species. The absorption (extinction) coefficient of the four different Hb species are plotted as a function of the wavelength of the incident light. Note that COHb and O_2Hb absorb red light similarly (black arrow). In addition, red light absorbance of MetHb and HHb are nearly identical (white arrow). and that MetHb absorb red and near-IR light equally well. Adapted from.[10] O_2Hb = oxyhemoglobin, HHb = deoxyhemoglobin, COHb = carboxyhemoglobin, MetHb = methemoglobin. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

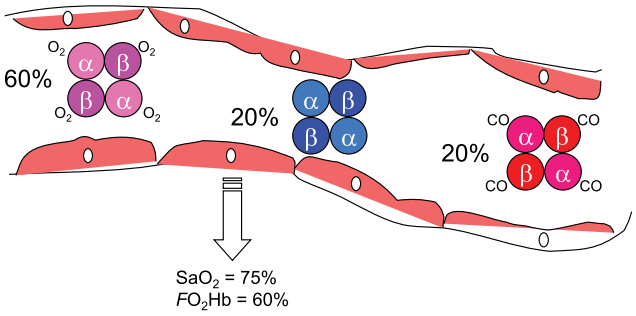

Figure 3 Distinction between SaO_2 and FO_2Hb content. Illustrated in this cartoon is blood comprised of 60% O_2Hb, 20% HHb, and 20% COHb. Since SaO_2 is defined as concentration of O_2Hb divided by the sum concentrations of O_2Hb and HHb, $SaO_2 = [60/(60 + 20)] \times 100 = 75\%$. In contrast, FO_2Hb content is defined as concentration of O_2Hb divided by sum concentrations of all Hb species, the FO_2Hb content $= [60/(60 + 20 + 20)] \times 100 = 60\%$.

Causes of falsely low or high SpO_2

Methemoglobinemia

Methemoglobinemia should be considered in patients with cyanosis, particularly in the presence of a normal or near normal partial pressure of oxygen (PaO_2).[41] Methemoglobin (MetHb) is formed when the iron (Fe) in the heme moiety is oxidized from Fe^{+2} to Fe^{+3}. MetHb impairs oxygen delivery to tissues by two distinct mechanisms: (i) MetHb itself is less able to bind oxygen and (ii) MetHb causes the oxygen dissociation curve of *normal* Hb to shift to the left which impairs unloading of oxygen at the tissue level — causing profound tissue hypoxia.

Hereditary MetHb is rare and is due to subjects having abnormal Hb (HbM) or having cytochrome b5 reductase deficiency. Most cases of methemoglobinemia are usually due to oxidizing chemicals or drugs such as nitrites, nitrates, aniline dyes, aniline derivatives (phenacetin, dapsone), sulfonamides, and lidocaine. Only 1.5—2 gm MetHb/dL of blood (a 10—20% of total Hb) can cause cyanosis. In anemic patients, cyanosis is less apparent because the corresponding absolute level of MetHb will be lower. MetHb levels between 20 and 45% can produce headaches, weakness, breathlessness, and altered mental status. Metabolic acidosis, dysrhythmias, and myocardial ischemia due to tissue hypoxia can also occur. MetHb levels between 50 and 60% are often fatal, presenting with hemodynamic instability, generalized seizures, and coma.

MetHb absorbs more IR than either O_2Hb or HHb (Fig. 2). Since its absorbance of red light is similar to HHb (Fig. 2), patients with significant methemoglobinemia can appear cyanotic and their blood very dark in color. Moreover, because MetHb absorbs both red and IR light equally well (Fig. 2), high MetHb levels result in an *R* value that approaches 1, which happens to be equivalent to a SpO_2 of 80—85%.[5,10] Therefore, high MetHb levels will cause the SpO_2 to trend toward 85%, resulting in an overestimation or underestimation of the SaO_2, depending on whether there is true hypoxemia that is <85% or normoxia, respectively. MetHb level can be directly analyzed by a co-oximeter. Treatment of methemoglobinemia includes stopping the offending agent, supportive care, and administration of a reducing agent such as methylene blue in severe cases, bearing in mind that methylene blue can cause spuriously low SpO_2.

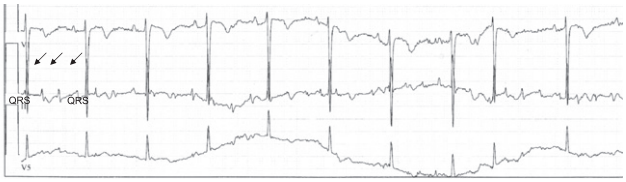

Figure 4 EKG rhythm strip of patient with spuriously low SpO_2 readings due to excessive motion. A three-lead EKG rhythm strip of the patient when the simultaneous pulse oximeter measurements noted a SpO_2 of ~40% and a heart rate of >200 beats per minute. Note the presence of smaller spikes (arrows) that corresponds to his tremor.

Sulfhemoglobinemia

Sulfhemoglobin (SulfHb) is formed by the irreversible oxidation of Fe^{+2} in the porphyrin ring of Hb to Fe^{+3} (similar to MetHb) but additionally has a sulfur atom incorporated into the porphyrin ring. It is most often caused by oxidizing drugs that may or may not contain sulfur; in the latter cases, it is thought that endogenous hydrogen sulfide (H_2S) derived from gut bacteria is the source for the sulfur, particularly in severely constipated states.[42] Hence, SulfHb may be formed by aniline dyes, acetanilid, phenacetin,

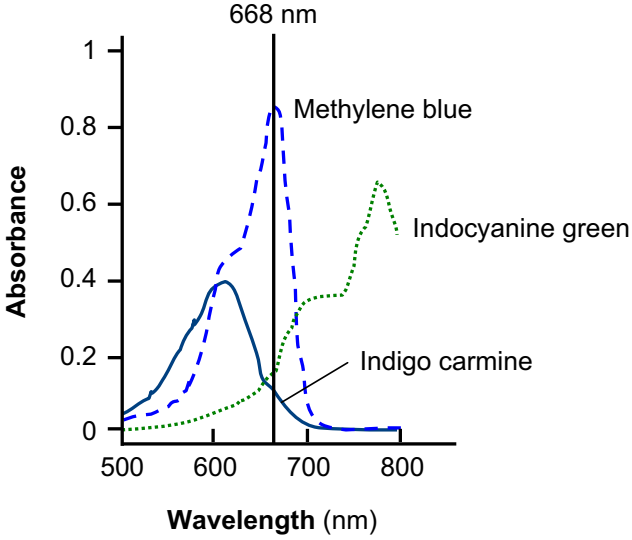

Figure 5 Absorption spectra for pigmented dyes used in medicine. The absorption of methylene blue, indigo carmine, and iodocyanine green are plotted as a function of the wavelength of the incident light. Note that the peak absorption of methylene blue (668 nm) is very close to the wavelength for red light (660 nm); hence, methylene blue absorbs red light very well and behaves more like HHb than either indigo carmine or iodocyanine green. Adapted from Ref.[23] (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

phenozapyridine, nitrates, sulfonamides, metoclopramide (structurally similar to aniline dyes), flutamide, dapsone, dimethyl sulfoxide (DMSO) or by exposure to sulfurated chemicals such as hydroxylamine sulfate used in various cleaning solutions.[42–45] SulfHb cannot carry oxygen.[46]

The major clinical manifestation of sulfhemoglobinemia is the presence of cyanosis. A mean capillary concentration of only 0.5 gm/dL (5 gm/L) of SulfHb is sufficient for detectable cyanosis (compared with 1.5 gm/dL for MetHb and 5 gm/dL for HHb). While SulfHb markedly reduces oxygen transport, it also shifts the *normal* Hb oxygen dissociation curve to the right, facilitating oxygen unloading in tissues. Note that this rightward shift of the normal Hb oxygen dissociation curve by SulfHb is opposite to that seen with methemoglobinemia, where O_2 unloading is impaired at the tissue level. Hence, sulfhemoglobinemia has fewer adverse clinical consequences than methemoglobinemia for the same level of concentration. Nevertheless, extremely high SulfHb levels will ultimately impair oxygen transport by reducing O_2Hb.

SulfHb has greater red light (660 nm) absorbance than HHb or MetHb.[43] Although it is not known precisely, SulfHb most likely has a similar degree of absorbance at red and near-IR light because there have been several reports that the SpO_2 of persons with severe sulfhemoglobinemia are ~85%, a sign that absorbance of red and near-IR light are similar with SulfHb, resulting in a *R* value that approaches 1 (as seen with methemoglobinemia).[42,43,45] While most co-oximeters have four wavelengths and are able to differentiate O_2Hb, HHb, COHb, and MetHb, they cannot specifically identify SulfHb. Moreover, significantly high levels of SulfHb are often falsely reported as MetHb as many spectrophotometers cannot accurately differentiate MetHb from SulfHb. In these instruments, additional biochemical testing is required to differentiate between SulfHb and MetHb; *e.g.*, SulfHb remains intact after addition of cyanide to the blood sample whereas MetHb disappears. However, newer generations of co-oximeters can differentiate between SulfHb and MetHb. In centers where determination of SulfHb levels are not available, unresponsiveness to methylene blue may be the only indication of sulfhemoglobinemia in patients initially presumed to have methemoglobinemia. There is no specific treatment for sulfhemoglobinemia (no known antidote available) other than eliminating exposure to the offending agent and supportive therapy. The concentration of SulfHb will decrease as erythrocytes are destroyed and replaced. For extremely symptomatic cases, exchange transfusion has been performed with success.[45]

Poor probe positioning resulting in decrease absorption of red and/or IR light

Poor probe positioning can result in light shunting wherein the emitted light bypasses tissues and strikes the photodetector. If both transmitted red and/or IR light are largely unabsorbed, the *R* value can approach 1 (see Red:IR Modulation equation above). As a result, similar to that seen with methemoglobinemia, the SpO_2 may either overestimate or underestimate the SaO_2.

In older models of pulse oximeters, ambient light complicated SpO_2 measurements by directly hitting the photodetector and/or by increasing the amount light going through the tissues, making the SpO_2 measurements unreliable. However, most modern pulse oximeters are able to "subtract" the ambient light signals. If effects of ambient light remain a concern, shielding the probe with an opaque material is a simple solution.

Sepsis and septic shock

There are conflicting studies on how SpO_2 is biased in the setting of sepsis and septic shock. Secker and Spiers[18] compared 80 paired SpO_2 and SaO_2 readings in patients with septic shock and showed that only in those with low systemic vascular resistance (as measured by a pulmonary artery catheter), the SpO_2 underestimated the SaO_2 by a mean of 1.4%, a level that was statistically significant but unlikely to be clinically important. These results are supported by a human study where induction of hyperemia in one arm of volunteers resulted in lower SpO_2 than the control arm.[47] A hypothesis to explain this phenomenon is that vasodilation from the sepsis resulted in creation of arteriovenous shunts that culminated in venous pulsations and spurious detection by the pulse oximeter of some venous blood as arterial[18,47] (as previously discussed).

By contrast, a retrospective review of 88 patients with severe sepsis and septic shock found that in those with hypoxemia (defined as $SaO_2 < 90\%$), SpO_2 significantly *overestimated* SaO_2 by nearly 5%.[48] In several studies examining critically ill patients with various acute illnesses, some found SpO_2 underestimated SaO_2 while others found the opposite (reviewed in Ref.[48]). Even in those studies that examined only septic patients, factors that may account for a difference in the direction in which SpO_2 is biased include differences in: (i) the extent of fluid resuscitation and tissue perfusion, (ii) sepsis-induced cardiac dysfunction, (iii) sites interrogated by the pulse oximeter probe, (iv) types of pulse oximeters and probes used, (v) vasoconstrictor use, and (vi) the presence of other co-morbid conditions that may spuriously affect SpO_2 values unpredictably. Thus, a number of variables that occur in patients with severe sepsis and septic shock make it difficult to predict which direction SpO_2 may be biased. Until more definitive studies are performed, it appears prudent to at least determine how well SpO_2 correlates with SaO_2 and FO_2Hb measurements in any unstable, critically ill, cardiopulmonary patient.

Causes of falsely low FO_2Hb as measured by a co-oximeter

Severe hyperbilirubinemia (~≥30 mg/dL) due to increased heme metabolism (hemolysis) or decreased bilirubin metabolism (liver disease)

With metabolism of each heme molecule, one molecule of bilirubin and one molecule of CO is produced. Bilirubin itself has minimal effect on SpO_2 measurements on standard pulse oximeters since this pigment has little or no absorbance of red and near-IR light. Because SpO_2 measurements by standard two-wavelength pulse oximeters are not

lowered by the presence of COHb, it could be presumed that SpO_2 can overestimate FO_2Hb in the presence of significant hemolysis (see sickle cell anemia). However, very high bilirubin levels can make co-oximeter measurements of FO_2Hb falsely low by *artifactually* increasing MetHb and COHb levels; thus, pulse oximetry measurements of oxygen saturation (SpO_2) may actually be more accurate than FO_2Hb in the presence of severe hyperbilirubinemia.[49,50] The degree the co-oximeter underestimates the FO_2Hb depends on the co-oximeter as different co-oximeters ultilize different sets of wavelengths. In contrast, SaO_2 should not be affected by hyperbilirubinemia since the determinants of SaO_2 are only O_2Hb and HHb (see Box 1).

In hyperbilirubinemia due to liver disease, there is no increase in heme metabolism and thus no increase in CO. Since the elevated bilirubin will still artifactually increase MetHb and COHb values on the co-oximeter, SpO_2 measurements will be even more accurate than co-oximeter measurements of FO_2Hb. However, it is important to note that most patients with hyperbilirubinemia have bilirubin levels that are not great enough to have significant impact on FO_2Hb measurements.

Fetal Hb (HbF)

The absorbances of red and near-IR light by HbF is essentially the same as HbA and thus SpO_2 measurement is as reliable in newborns as in adults. However, HbF may be misread as COHb by co-oximeters, thereby spuriously lowering the FO_2Hb.[51] The degree to which HbF affects FO_2Hb readings depends on the specific co-oximeter used as different co-oximeter models often utilize different sets of wavelengths; in addition, HbA and HbF differ in light absorbance (for both O_2Hb and HHb) primarily in the 450—650 nm spectral range — which coincides with the wavelengths used by most co-oximeters.[52,53] Although simply adding the *fictitious* COHb level to O_2Hb in an attempt to correct the FO_2Hb (provided there is no evidence of hemolysis or CO poisoning that can cause a true increase in COHb) may work for some systems, some co-oximeters can correct the readings in the presence of HbF. While using the oxygen dissociation curve to derive a *calculated* SaO_2 from the PaO_2 is another option, this can be inaccurate as the oxygen dissociation curve for HbA and HbF can significantly differ throughout the SaO_2 span; more specifically, the p50, defined as the PaO_2 which correlate with a SaO_2 of 50%, is 19 mmHg for HbF and 27 mmHg for HbA. Thus, in the presence of HbF, the SpO_2 is at least as accurate, if not more so, than co-oximeter-derived O_2 saturations. Given the variability of how co-oximeters assess SaO_2 in the presence of HbF, clinicians and blood gas technicians should have a practical and mutual understanding of how co-oximeter results may be affected by HbF at their particular institutions.

Summary

Pulse oximetry is based on the principle that O_2Hb absorbs more near-IR light than HHb, and HHb absorbs more red light than O_2Hb. Under optimal conditions, pulse oximeters do not calculate SpO_2 of venous blood (and other stationary tissues) but rather only arterial SpO_2 by determining *changes* in absorbance of the light transmitted over time; *i.e.*, arterial blood volume changes with the cardiac cycle whereas the volumes of light absorbers in non-arterial tissues are relatively constant. Since pulse oximeters are calibrated for SpO_2 between 70 and 100%, displayed values below 70% should only be considered qualitatively accurate and not quantitatively. Inaccurate SpO_2 readings can occur with conditions that decrease arterial blood perfusion. The SpO_2 can overestimate FO_2Hb content in blood that contains increased amount of CO. In sickle cell anemia-associated vasoocclusive crises, SpO_2 can overestimate the FO_2Hb (due likely to the presence of increased endogenous production of CO) but could underestimate the SaO_2 (due to vasoocclusion-induced underperfusion). Falsely low SpO_2 can occur with venous pulsations, excessive movement, pigmented dyes, and certain dyshemoglobins. Although severe anemia *per se* does not cause a falsely low SpO_2, its presence can cause the SpO_2 to underestimate the SaO_2 in someone with true hypoxemia. SpO_2 can either overestimate or underestimate the SaO_2 with methemoglobinemia, sulfhemoglobinemia, and poor probe positioning. Sulfhemoglobinemia can mimic methemoglobinemia clinically and by SpO_2 and SaO_2 measurements. Finally, it is important to emphasize that even in the most optimal patient-pulse oximeter interface and settings, a completely normal SpO_2 does *not* rule out gas exchange problems in the lungs or the adequacy of ventilation since the alveolar-arterial oxygen difference and $PaCO_2$ are not measured by pulse oximetry.

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Conflicts of interests

None declared.

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